Is There a Safe Level of Lead Exposure?

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Earlier today you heard that man's environment contains lead in many forms and in many places. Since it is an element contained in the earth's crust in an average concentration of 16 parts per million, it has always been present in the environment even before the time when we could call it *man's* environment. This ubiquitous element is then absorbed from the soil along with other trace elements by plants and animals which may in turn form the diet of man. Thus man as well as the animals and plants has a certain "background" level of lead which is derived from the food he eats. This background level fluctuates in amount from place to place in the world depending upon the local concentration of lead in the soil. To this background level of lead is added lead derived from man's activities in mining, smelting, manufacturing and using lead and lead-containing products. Thus lead, unlike most other pollutants, has two significant sources, one natural and one derived from man's activities. The lead from the natural sources tends to gain entry to the body through the intestinal tract with the respiratory system playing a relatively unimportant role as a route of absorption. While in contrast to this, lead derived from man's industrial activity tends now to enter the body more through the lungs than the mouth, although as in the case of childhood lead poisoning, there are exceptions to this rule.

Today I have been asked to discuss the question "Is there a safe level of lead exposure?" and since for the reasons I have just given, it is, and always will be, impossible to prevent some exposure to lead, it will be comforting for all os us if I can answer the question affirmatively and state that there *is* a safe level of lead exposure. If, however, by the word "safe" we mean absolutely safe for everyone everywhere, a difficulty arises, since to be completely safe, one must at the very least have a complete absence of harm, and proving the complete absence of something cannot be done. No analyst, however expert and provided with the finest equipment, will ever be capable of detecting *nothing*. The problem is not that an absolutely safe level of lead may not exist, it is that it is logically impossible to prove it. The same problem is faced by all of us who pass on the safety of materials, structures, food additives, radiation standards or our daughter going "solo" in the family car. Absolute safety is impossible, and if we are to discuss anything less than absolute safety, as I believe we are forced to do, we must discuss what level of risk is acceptable in a given situation. This is not to advocate a reckless or callous attitude, since we may choose to set the acceptable level of risk very low indeed as in designing a skyscraper to resist high winds, or we may choose a higher level of risk as when we go skiing or mountain climbing. Our view of what is an acceptable level of risk may also

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Table 1.–Cases of plumbism among battery workers in areas having different lead exposures.

	Atmospheric Lead Concentration (M Pb/10 m^3 in air)			
	0-0.74	0.75-1.4	1.5-2.9	>3
Men Exposed	97	84	168	125
Men with early plumbism	4	6	50	67
Percentage affected	4.1	7.1	29.8	53.6

change with time. For instance, society's attitude to the acceptable risk attached to particular occupations has changed with time. In 1700 Ramazzini wrote in his book, DISEASES OF WORKERS, "The mortality of those who dig minerals in mines is very great, and women who marry men of this sort marry again and again. According to Agricola at the mines in the Carpathian Mountains, women have been known to marry seven times." Today we regard this type of occupational mortality with horror.

Another much more trivial example of a change of attitude with time is the burning of leaves in the fall. The smell of those burning leaves used to be part of the pleasure of the fall, as much a part of it as the autumn colors. Now we worry about the particulate loading of the air, the carbon dioxide causing melting of the polar ice cap, etc., and yet the leaves are the same leaves; the pyrolysis products from burning them are the same. But society has changed its way of looking at the smoke.

As society gradually raised its standards for deciding what was an acceptable risk, it became more and more important to refine the tools used in measuring the risk and of factors associated with it. This is illustrated by Table 1 in which the number of cases of mild lead poisoning are correlated with the level of lead in the air of the part of the factory in which they worked. In this table it can be seen that in the highest exposure area over 50% of the men are suffering from the early signs of lead poisoning. This had been an occupational risk of working with lead which had been recognized and accepted for centuries, but now as it became clear for the first time that the level of lead in the air was directly related to the sickness rate, it became possible to suggest ways of reducing the amount of illness by reducing the amount of lead inhaled by the workmen. In England this approach led to a reduction in the notified cases of lead poisoning from 1,058 in 1900 to 239 in 1928, despite a large increase in the tonnage of lead used over these years. Society had said lead poisoning was no longer a necessary or acceptable cost of doing certain types of work.

However, as in many fields of human endeavor, it is one thing to know *how* to reach a particular goal, but often quite another to actually achieve it. So it is with the problem of preventing occupational disease due to lead. We know *how* to prevent it, and in many plants the worker is safer at work than he is at home, but in other factories knowledge or funds or both have not been brought to bear on the problem as they should.

With the practical ability to prevent acute lead poisoning by setting safe levels of lead in the air which should not be exceeded, it was a logical next step to consider the effects of long exposures lasting over 20-30 years.

Such studies are difficult and time-consuming, but in one such study reported from an electric storage-battery works in 1963, the health of employees with two different levels of lead exposure was studied, and in Table 2 the results of the portion of the study having positive findings are set out. The groups marked A and B are workers with little or no occupational exposure to lead, while group C represents a high-exposure group. The men in group C had an average rate of lead excretion in the urine of about 250 μg Pb/l of urine, and these levels had been maintained or exceeded for 20 years or more. The results show that there was an excess of actual deaths over the

Table 2.–Expected and observed deaths from cerebral hemorrhage, cerebral thrombosis, and cerebral arteriosclerosis in pensioners, 1926-1961, and in employed men, 1946-1961.

		Grade of Exposure					
	Year of	Low		Low		High	
Group	Death	Expected	Observed	Expected	Observed	Expected	Observed
Pensioners	1926-1950	0.7	0	0.2	3	0.8	5
	1951-1961	7.2	6	3.2	3	8.5	19
	1926-1961	7.9	6	3.4	6	9.3	24[a]
Employed	1946-1961	3.2	3	3.1	3	5.6	9

[a] $X^2 = 21.7$ $p < 0.001$

expected number of deaths among the high-exposure group, but not in groups A and B.

The expected number of deaths was calculated from the death rates prevailing for all males adjusted for age. The conclusion of the authors is that among 425 pensioners of this battery plant, of whom 184 had died during the period covered by the study, there was a significantly greater number of men dying of cerebrovascular disease such as strokes, brain hemorrhages, etc. than in the lesser exposed group. Analysis of the data has shown moreover that, as the lead exposure had decreased with improved working conditions, the excess of cerebrovascular disease had diminished. This study, dealing as it did with a severe lead exposure over a long period of time, is in contrast to a study carried out in Wenatchee, Washington, amongst apple orchard workers who were involved in the spraying of lead arsenate as an insecticide. The urine lead values for the 3 exposure groups shown in Table 3 are not as high as those sometimes seen in other industrial exposures, but they are of particular importance for this reason, since the urine lead concentrations range from those slightly more than are commonly found in urban communities to those found in moderate lead exposures in industry. Among the factors studied in assessing the health of the orchardists were weight, blood pressure, diseases of the cardiovascular system, skin disorders, eye irritation, chronic nervous diseases, blood diseases, kidney disease, pulmonary tuberculosis, visual acuity, syphilis, neoplastic disease, and fertility.

Each factor was studied to find out whether it had been modified by the lead arsenate exposure. By comparisons between groups and with other nonexposed populations, no evidence was found that any of these factors was altered by the lead arsenate exposure. In this study special attention was given to medical examination of children because, in the Wenatchee area where orchards surrounded the communities or the houses in which they lived, there were unusual opportunities for children to be exposed to lead arsenate insecticide sprays and spray residues on branches, leaves, and grass in addition to lead arsenate spray residues they ingested on apples. There was only one respect in which these children differed from children in other districts. Their urinary lead and urinary arsenic values were nearly twice as high as the corresponding values for a control group of children taken at the same time in Washington, D.C. (who had a mean urine lead level 0.026 mg/Pb/l S.D. 0.0128.) There was no indication of adverse effects of lead arsenate exposure on the health of the Wenatchee children.

While this study of persons exposed to lead arsenate has some deficiencies when used as a source of information on the possible biological effects of other forms of lead, it is particularly important for 2 reasons. Firstly, it is one of the few modern studies containing an appreciable number of women of childbearing age; and, secondly, it is one of the few studies having children with a lead exposure other than flaking lead paint. Society's attitude to the risks to health that are acceptable as a result of a person's occupation or of merely living in a community have gradually changed over the centuries until at the present time they have received their best exposition in a statement by the World Health Organization, which states that levels of pollutants should be set at a level that safeguards health, and health is defined as a state of complete physical,

Table 3.—Urine lead values of persons in Wenatchee study classified by severity of exposure.

Group		Urinary Lead µg Pb/l No. of Analyses	Average	SD	Blood Lead µg Pb/100 g blood No. of Analyses	Average	SD
Low exposure group							
	Men	146	35	21	148	26	11
	Women	123	28	19	124	26	10
Intermediate exposure group							
	Men	102	43	30	108	30	11
	Women	25	27	15	27	22	10
High exposure group							
	Men	386	88	60	329	44	16
	Women	61	46	25	58	34	13
Children under 15							
	Boys	81	53	39	17	37	15
	Girls	65	54	40	14	36	10

mental, and social well being and not merely the absence of disease or infirmity.

I have attempted in the time available to show that man has passed through 3 stages in learning about the biological effects of lead. The first stage, which lasted until about the 3rd century B.C., was the recognition of a diseased state or clinical picture but without assoicating it with the causative agent — lead. In the 3rd century B.C., the relationship between lead and a specific clinical state was recognized, and finally in the 19th century it was found that large doses of lead caused severe disease and progressively smaller doses of lead caused progressively less and less illness until a state was reached that appeared to be "normal health" as defined by the World Health Organization statement. It is possible but unlikely that this more or less happy state would have continued until the present time if the chemical analysts had not developed such refined methods for dissecting the biochemistry of the body. By doing so, they have raised a host of questions, many of which are not answered at this time. In particular the questions: When is a biochemical change a deleterious change? Can a biochemical change by itself be taken as evidence of ill health if by our best abilities we can find no interferences with a person's physical, mental, or social well being? These questions are not confined to the effects of lead, and as we are given more and more refined analytical techniques with the ability to detect smaller and smaller changes within the body, many more substances that are now considered harmless at present levels will be found to cause such changes. How do we sort out which changes are merely reflecting absorption, which changes show adaptation to the presence of a chemical, which changes demonstrate compensation by the body, and which changes are correlated with a true threat to health? It is apparent that our ability to measure biochemical changes has in many instances outrun our ability to understand the significance of the changes we observe. In the case of lead this question arises particularly with regard to its effect on the synthetic pathway of hemoglobin synthesis. To produce a molecule of heme which later combines with the protein globin to form the hemoglobin in the red cell, a series of synthetic steps are required. Each one of these steps is facilitated by a specific enzyme, the activity of which may be altered by a number of factors. Lead exerts an inhibiting effect on several of these enzymes, although the sensitivity to this lead effect varies considerably from enzyme to enzyme. The enzyme which exerts the controlling influence on the rate at which the whole synthetic process can proceed is heme synthetase. Anemia as a result of inhibition of heme synthetase is not seen in otherwise healthy adults until the lead level in the blood rises to about 110 µg PB/100 g blood. The blood lead level commonly found in persons in North America is

between 13 and 30 μg PB/100g blood. At levels below 110 μg of lead in the blood, while anemia is not found, effects on the heme synthetic pathway can be detected.

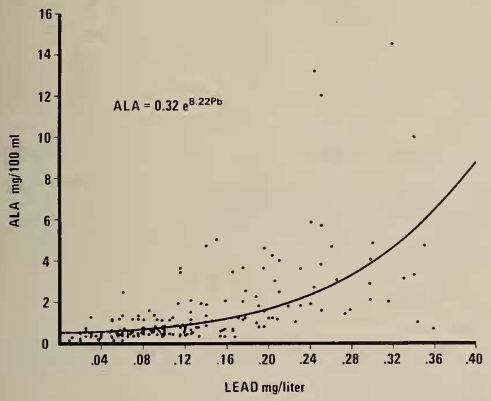

Fig. 1. – 193 men exposed to inorganic lead. Regression: ALA on lead in the urine.

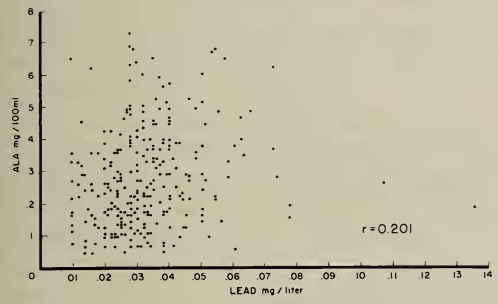

Fig. 2. – 298 Du Pont office workers. Regression: ALA on lead in the urine.

The first of these effects which was found to occur at relatively low levels of lead was the presence of delta-aminolevulinic acid in the urine. Fig. 1 shows the relationship between the level of lead excretion in the urine and the level of delta-aminolevulinic acid in the urine. The important point to notice here is that as the lead level falls to within the normal range, the effect upon the excretion of ALA becomes virtually nil. This point is amplified in Fig. 2 which, instead of dealing with values derived from lead workers, deals with the findings in 298 office workers. This table uses an expanded scale and represents the area covered by the left-hand corner of Fig. 1. The lead levels are those found in a normal urban population, and there is no effect of lead on ALA excretion in this range of lead values. The other determination that has recently become a matter of considerable interest in discussing the effects of lead upon the body is the enzyme ALA dehydrase. The activity of this enzyme when measured in red cells shows a strong negative correlation with the level of lead in the blood. The interest in this enzyme has centered on the fact that the enzyme shows a reduction of activity at levels of lead which must be considered within the "normal" range. This might seem to be clearly a deleterious effect of lead and yet, anemia is not seen until the blood lead reaches levels above 110 μg/100g blood, at which level the activity of the enzyme is barely detectable.

In considering the safety of levels of lead in the blood that cause appreciable depression of ALA dehydrase activity, it is not enough to consider the steady-state condition, because it can be argued that, although a person is manufacturing enough hemoglobin to satisfy his normal day-to-day needs, he might not be able to cope with the need to create large amounts of hemoglobin to replace sudden severe blood loss such as might occur in an automobile accident. Therefore to investigate this condition we carried out an experiment using dogs and simulated a massive bleeding situation. Thirty-six dogs were divided into 3 groups of 12. One group was kept as a control group, while the other 2 were given lead acetate in the diet. The first group of dogs was given 100 ppm lead acetate in the diet and the second 500 ppm.

These levels of lead were maintained in the diet for 31 weeks, at which time the ALA dehydrase activity of the dogs on the highest level of lead was 16-28% of the level prevailing before they were given lead. Since, at this thirty-first week, the enzyme activity was not as low as we desired, the amount of lead in the diet of this group of dogs was doubled for the next 16 weeks. During this final prehemorrhage period the blood lead levels in these dogs receiving the high level of lead averaged 60-80 μg Pb/100g blood, and their enzyme activity varied between 0.5 units/ml of red cells to being undetectable. Thus, when detectable, the enzyme level was about 2% of that found prior to feeding

lead, while the group of dogs given the 100 ppm lead in the diet showed a 50% reduction in ALA dehydrase activity. At the end of 46 weeks of lead feeding, there was no evidence of any difference in the health of the dogs in any of the groups by any of the usual biochemical, clinical, or behavioral standards. Each of the dogs was then bled under sterile conditions and in a similar manner to the methods used in a human blood donation center until each dog had lost one-half of his blood volume. The recovery of the dogs to normal hematological values was then followed with frequent measurements of the hemoglobin, reticulocyte counts, and hematocrit, and no difference in recovery rates between any of the groups was seen. Indeed, so close were the data when plotted on graphs that the curves for the 3 groups of dogs were superimposed. These dogs regained their normal hemoglobin levels within 4-7 weeks, which other investigators have found to be the normal time for complete recovery from a severe hemorrhage. This experiment demonstrates that recovery from the loss of one-half of the circulating blood volume in dogs is not hampered by having very low or immeasurable levels of the enzyme ALA dehydrase. I believe the interpretation of these results based on our present state of knowledge would be that there is a vast excess of this enzyme in the body, and it is perfectly possible to get along with 1-2% of the normal amount without any apparent harmful effect on health. I am not suggesting that we ignore the relatively small changes in the enzyme level that can be found at the levels of lead commonly found in the United States population, but I *am* suggesting that to base air-quality standards on this type of data, as has recently been done, may be logically defensible but is scientifically questionable.

The whole field of the effect of the environment on man and the effect of man on the environment suffers at the moment from a lack of a sense of proportion. Not all effects are equally bad. In fact, we lack a basis for making value judgements such as "good" or "bad" about a great many of the changes we can now measure. This is not a plea for inaction while we do more research, but that while we have so many obviously major problems in society, let's not be afraid to say some effects that we are now capable of detecting are more important than others. Even within the field of air pollution it is very likely that at the present time there is more total illness caused by natural air pollutants such as pollen and mold spores than by man-made pollutants such as sulfur dioxide and oxidants. Again this is no reason for inactivity, but let's adjust the intensity of our activity to the relative size of the problems.

In considering the safety of any particular level of lead, one must be alert to the possibility that there are groups of persons in the population who are more sensitive to the effects of lead than are most people. This problem underlines my earlier remarks on absolute safety, since a categorical statement that a particular level of lead is absolutely safe would mean that nowhere does there exist a person who is particularly susceptible to the effects of this level of lead. Obviously, if rigorously interpreted, this would involve testing everyone's susceptibility to lead, which is manifestly impossible. Therefore, we are forced to base our statements on a sampling of the total population. While I cannot lay before you all of the data upon which you can base your own opinion, I believe a fair summary of our present state of knowledge would be as follows. In the 19th and early 20th centuries, when some occupations such as lead glazing of pottery carried a high exposure to lead, there was some evidence that women might be more susceptible to lead than men, but the effect was far from clear and was complicated by differing work habits, differing economic states, and differing nutritional states between the men and women employed in these industries. In more recent times these gross exposures to lead have virtually disappeared, and opportunities for valid comparisons between the reactions of men and women to the same level of lead have been very rare. I believe the comments made by the authors of the report on the

Wenatchee orchard workers with respect to fertility can also be applied to the problem of whether men or women are more susceptible to lead. They say, "The instances reported in the literature of an effect of lead on human fertility appear to be limited to men and women who were far more heavily and much more regularly exposed to lead than the residents of Wenatchee." It would appear that a clinical state approaching that of frank lead poisoning is necessary before the fertility of men and women is affected. I would add that similar conditions seem to have to prevail to demonstrate a difference in reaction between men and women to a given amount of lead. While it is true that children may exhibit more alarming symptoms and face a more grave prognosis when suffering from lead poisoning, it is also true that the dose of lead which the child ingested was usually many fold greater in proportion to his size than that received by most adults suffering from lead poisoning. The mean daily fecal output of lead by the lead-poisoned children in Chisolm's series (44 mg Pb/day) exceeded by approximately 6-fold that of a group of severly exposed industrial workers (7.6 mg Pb/day). There are many other facets of the problem of special sensitivity which can quite properly be raised such as: Are persons with special diseases or the elderly more sensitive to lead? And the answer at this time has to be that in the thousands of years of man's experience with lead, such groups have not been uncovered, but it is possible that with more refined diagnostic tools such groups may be found in the future. This is not the same as saying that because we don't know for certain that such groups do not exist that there is a high probability that they will in fact be found.

I have attempted to deal with the problem of safe levels in a manner that raises issues common to many chemicals in our environment. For instance, in a review article on "Mechanisms of Oxygen Toxicity," by Niels Haugaard, his opening words are "Except for organisms especially adapted to live under anaerobic conditions, all animals and plants need oxygen for the production of energy and maintenance of life. Yet oxygen is toxic to life at concentrations only slightly greater than that found in air." In fact it would be just as difficult to answer the question, "Is there a safe level of oxygen?" as it is to answer the question, "Is there a safe level of exposure to lead?" If we are to set a safe level of lead exposure based on biochemical changes we cannot interpret, we are setting in train a series of events which have their impact not only on economics, social patterns, and our natural resources, but also on biological systems.

We are, as members of society, often counselled to make no moves affecting our health and welfare, the consequences of which are not completely understood and yet we find these same councellors often surprisingly willing to advocate crash programs to remedy some real or imaginary threat. All agents in the environment that can under certain conditions cause harmful effects are not equally hazardous, and I firmly believe that a sensible plan of attacking the most important items first can be drawn up, provided the facts are allowed to speak for themselves. I believe that lead poisoning in children constitutes a definable problem of considerable seriousness about which something useful can be done. Since our resources are finite, I would put this item far ahead of the threat to health from other sources of lead in the environment.